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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,156	12/03/2001	Thomas Honger Callisen	5885.204-US	1686

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EXAMINER	
NASHED, NASHAAT T	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,156	CALLISEN ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *18-39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/3/01 & 4/26/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The application has been amended as requested in the communication filed January 29, 2004. Accordingly, claims 1-17 have been canceled, and new claims 18-39 have been entered.

The use of the trademark LIPOLASE® has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

> The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 18-39 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) The phrases "modified by having two or three" in claim 18, and "has an amino acid sequence having two or three amino group" in claims 19, and 25 render the claims indefinite and confusing because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. The word "having" in both phrases has two meaning in the claims. The first is lipase in which two or three residues are chemically modified with hydrophobic groups, whereas the second is a lipase, which comprises two or three residues modified. The second meaning includes modifying more than two or three residues. For examination purposes only, the second and broader meaning is assumed in interpreting the claims.

(b) Claim 24 is incomplete because it omits essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: (a) treating a lipase with a dervatizing agent; and (b) purifying the derivatized lipase from the reaction mixture.

(e) The phrase "change number and/or position" in claims 30 renders the claim indefinite because the resulting claim does not clearly set forth the

metes and bounds of the patent protection desired. The "number" of an amino acid residue defines the "position" of said amino acid in an amino acid sequence, and thus, the word "number" and "postion" in presumably an amino acid sequence are referring to the location of an amino acid residue in an amino acid sequence. The presence of both word would confuse one of ordinary skill in the art because applicant is attempting to distinguish between the two. The deletion of "number" or "position" would obviate this rejection.

(d) Claims 20-23, 26-29, and 31-39 are included in this rejection because they are dependent on rejected claims, and do not cure their deficiencies.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 18, 21-23, 24, 27-29, and 36 are rejected under 35 U.S.C. 102(b) as anticipated by Svendsen *et al.* (WO 92/05249).

Svendsen *et al.* teach lipase variant type I in which one or more aspartic acid residues of the lipid contact zone of the lipase are substituted by glutamine, aspargine, alanine, leucine, valine, serine, threionine, lysine or arginine, see page 6, lines 16-21. Specifically, they teach the mutations in *Humicola lanuginosa* lipase, see pages 7 and 8. Also, they teach the deletion of one or more amino acid residue, see from the last paragraph of page 9 through the first paragraph on page 13. The mutants taught by Svendsen *et al.* meet all the limitation of the claimed modified lipolytic enzyme of claims 18, and 21-23. The substitution of aspartic acid or glutamic acid with alanine, leucine, or valine results in linking covalently one of the hydrophobic groups methyl, 2-methylpropyl, or isopropyl, respectively, to the enzyme. Even, the substitution of

aspartic or glutamic acid residue would meet the limitation of the claims because the lysine side chain contain an additional $(CH_2)_3$ and $(CH_2)_2$, respectively, covalently attached to the lipase. Also, they teach substitution of one or more neutral amino acid residues with lysine or arginine, see the top of page 8. In addition, Svendsen *et al.* teach a method of preparing the lipolytic enzyme by mutagenisis (claims 24, and 27-29), see page 13 through19, as well as the use of the modified lipase in detergent composition (claim 36).

Claims 18, 21-23, 24, 27-29, and 36 are rejected under 35 U.S.C. 102(e) as anticipated by U. S. P. 5,869,438 ['438, (Svendsen *et al.*)].

The '438 patent teaches several variants of *H. lanuginosal* lipase in which 2 or 3 hydrophobic groups have been introduced to said lipase by site directed mutagensis which produced a lipase with improved wash performance, see Tables 4-7. As indicated above, the substitution of an aspartic or glutamic acid residue with lysine results in the introduction of a longer carbon side chain, a hydrophobic group, (18, and 21-23). Also in the patent reported are single and multiple deletion mutants, which would be expected to change the number of the amino acid following the deleted residues, see the paragraph-bridging column 13 and 14. In addition, the '438 patent teach a methods of identifying the residues to be mutated and deleted as well as method of making the various mutants (claim 24, and 27-29), see examples 1-22, as well as the utilization of the variant lipase in a detergent composition (claim 36).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 18-20, 23-26, and 29 rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over any of Murakami *et al.*

[IDS reference: JAOCS, Vol. 70 (6), pp.571-574 (1993)]; Basri *et al.* [JAOCS, 1992, Vol. 69 (6), pp. 579-583]; and Inada [U. S. patent 4,645,741 ('741)].

Murakami *et al.* teach the chemical modification of a lipase from *Phycomyces nites* containing 11 lysine residues and the amino group of the N-terminus using the water-soluble acylating agent, *p*-dimethylsulfonophenyl ester of fatty acids (DSP), see Figure 1. Also, they teach a method of preparing the chemically modified enzyme lipase at a free amino group, last paragraph on page 571, and an assay to monitor the level of modification, see page 572, the first paragraph after Figure 2. They teach the level of modification can be controlled by the molar ratio of the lipase and DSP as well as by the time of reaction and reported several derivative of said lipase wherein the lipase is modified between 38%-81%, see page 572, right column 572, second paragraph, and Table 1. Also, they teach various physicochemical properties of the modified enzyme including higher transesterification activity in organic solvent among others, see the results and discussion section.

Basri *et al.* teach a method of chemical modification of *Candida rugosa* lipase with imidoester hydrochlorides, see abstract, and the third paragraph, and that the lipase is derivatized to different degree by varying the molar ratio of the imidoester with respect to the enzyme, right column, on page 579. Also, the teach various physicochemical properties of the modified enzyme such as higher thermal stability relative to the native enzyme, and higher activity in organic solvent among others, see the results and discussion section.

Inada teaches the chemical modification of *Pseudomonas fluorescence* lipase using polyethelenglychol (PEG) and derivatives thereof, see columns 2-4 and examples 1-6. He teaches that, while unmodified lipase is not soluble in organic solvent such as benzene, toluene, and chloroform, the modified lipase is quite soluble and has a high activity.

The method of lipase modification and the modified lipase taught by Murakami *et al.*, Basri *et al.* and Inada appear to be identical to claimed method of lipase modification and modified lipase of the current invention. Claims 18-20, 23-26, and 29 are directed to a method of chemically modifying a lipase and the product of the method. The fact that the lipase may contain 6-12 amino group does not mean that all free amino groups are of equal chemical reactivity toward acylation, and therefore all of them will be expected to be acylated. If accessible to water, the amino terminus is the most reactive at neutral pH's because its partially or mostly unprotonated (pK_a 6.8-8.0), whereas the amino group of a Lysine residue is mostly protonated at neutral (pK_a 10.4-11.1). Lysine residue in a protein may or may not be accessible for chemical reagents to react with, and their actual pK_a is highly dependent on their individual local environment in the protein such as proximity to charged group and solvent. Only amino groups accessible to solvent and having sufficient chemical reactivity toward an acylating agent under a given condition will be acylated. While the number of acylated amino groups in the

lipase taught by any Murakami *et al.*, Basri *et al.* and Inada is unknown, the level of acylation can be controlled as described in the cited prior art. Also, since the claims read on a modified lipase comprising 2 or 3 chemically modified residues, the claims read on any number of modified lipase at more than two amino groups. Thus, claims 18-20, 23-26, and 29 are rejected under 35 U.S.C. § 102(b).

These rejections are being made under 35 U.S.C. § 102(b) and 35 U.S.C. § 103 because it is not possible for the Examiner to physically compare the claimed chemically modified lipase and method, and those reported by Murakami *et al.*, Basri *et al.* and Inada. Applicants bear the burden of providing evidence, which distinguishes the claimed method and modified lipase from those disclosed by Murakami *et al.*, Basri *et al.* and Inada. A preferred means of providing this evidence is for applicant to submit a side-by-side comparison between the modification method and modified lipase of the prior art and the claimed method and modified lipase which demonstrates any material differences and shows the claimed modified lipase to be distinct and unobvious in view of the enzymes of the prior art. *In re Best, Bolton, and Shaw* 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald, Sanders and Bagheri* 205 USPQ 594 (CCPA 1980).

Claims 21, 22, 27, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boel *et al.* (IDS reference: EP 305 216 B1) in view of the prior art as exemplified by Murakami *et al.*, Basri *et al.*, and Inada, and the commercial availability of *Humicola lanuginosa* (LIPOLASE from NOVO NORDISK A/S, admitted prior fact, see the specification on page 1, line 10-11).

Boel *et al.* teach the cloning of *H. lanuginosa* lipase and report the amino acid sequence as well as the cDNA encoding said lipase, see Figures 5a and 5b. Also, they teach a recombinant method to making the lipase in large quantity, see example 3 and 4 on page 12. The table on page 11 reports the amino acid composition of the lipase, which includes 7 lysine residues.

The teachings of Murakami *et al.*, Basri *et al.*, and Inada are summarized above.

Any of Murakami *et al.*, Basri *et al.*, and Inada provides one of ordinary skill in the art to acylate a lipase with the acylating agents to produce a lipase having higher activity in catalyzing transesterification reaction in organic solvent. The commercial availability of *H. lanuginosa* lipase would have been further motivation to the ordinary skill in the art to use said lipase to make the acylated lipase. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to purchase the LIPOLASE preparation from NOVO NORDISK A/S and modified by the method described by Murakami *et al.*, Basri *et al.* or Inada (claims 27 and 28) to produce the modified *H. lanuginosa* lipase (claims 21 and 22). Since *H. lanuginosa* lipase contains seven lysine residues and one N-terminus amino group, one of ordinary skill in the art would have had a reasonable expectation of success in obtaining the modified lipase.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

Claims 18-33, and 35-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over U. S. P. 5,869,438 (Svendsen *et al.*, '438) in view of Murakami *et al.*, Basri *et al.*, Inada, and Olesen *et al.* (IDS reference WO 94/04035)

The teaching of '438 patent, Murakami *et al.*, Basri *et al.*, and Inada is summarized above.

Olesen *et al.* teach the addition of lipase to dough improves the properties of dough and baked products, see the abstract.

The '438 patent provides one of ordinary skill in the art with motivation to make the variant lipases as they teach that the variant lipases have higher thermal stability and higher specific activity than those of the wild type, see examples 24 on page 43. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to make mutant lipases as taught by the '438 patent which including change the number and/or positions of amino, thiol, hydroxyl or carboxyl groups including the mutation of lysine-46 to arginine, see for example Table 6, and derivatize the newly added amino group as described by any Murakami *et al.*, Basri *et al.*, and Inada (claims 18-33 and 35). It would have been further obvious to the ordinary skilled in the art to utilize the derivatized lipases in detergent composition as taught in '438 patent (claim 36 and 37). In addition, Olesen *et al.* provide one of ordinary skill in the art with motivation to use lipases to prepare dough and baked products as they teach that the addition of lipase to dough ingredient improves the dough properties, see at least the abstract. Thus, it would have been further obvious to one of ordinary skill in the art at the time to utilize the derivatized lipase in a method to make dough taught by Olesen *et al.* to make a dough with improved properties (claims 38 and 39). Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

Claims 18-30, 31, 33, and 35-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Svendsen *et al.* (IDS reference: WO 92/05249) in view of Murakami *et al.*, Basri *et al.*, and Inada, Olesen *et al.* (IDS reference WO 94/04035)

The teaching of Svendsen *et al.*, Murakami *et al.*, Basri *et al.*, and Inada is summarized above.

Olesen *et al.* teach the addition of lipase to dough improves the properties of dough and baked products, see the abstract.

Svendsen *et al.* provide one of ordinary skill in the art with motivation to make the variant lipases as they teach that the variant lipases has higher thermal stability than

that of the wild type as well as improved wash properties, see example 19 on page 43. Thus, it would have been obvious to one of ordinary skill in the art to make mutants as taught by Svendsen *et al.* which including change the number and/or positions of amino, hydroxyl or carboxyl groups and derivatize the newly added amino group as described by any Murakami *et al.*, Basri *et al.*, and Inada (claims 18-31, 33 and 35). It would have been further obvious to the ordinary skilled in the art to utlize the derivatized lipases in detergent composition as taught in Svendsen *et al.* (claim 36 and 37). In addition, Olesen *et al.* provide one of ordinary skill in the art with motivation to use lipase to prepare dough and baked products as they teach that the addition of lipase to dough ingredient improves the dough properties, see at least the abstract. Thus, it would have been further obvious to one of ordinary skill in the art at the time to utilize the derivatized lipase in a method to make dough taught by Olesen *et al.* to make a dough with improved properties (claims 38 and 39). Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 18-33, and 35-39 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1-51 of U.S. Patent No. 5,869,438 in view of in view of Murakami *et al.*, Basri *et al.*, Inada, and Olesen *et al.* Claims 1-51 are directed to various multiple mutants of a lipase in cluding that from *H. lanuginosa*. The mutants include substitution of aspartic and glutamic acid with lysine, serine, and arginine among others including the mutation lysine46 to arginine. As indicated above, one of ordinary skill in the art would have been motivated to derivatize the mutants taught in the'438 patent as described by any of Murakami *et al.*, Basri *et al.*, and Inada to provide lipases capable in carrying out a transesterfication reaction (claims 18-33 and 35). The ordinary skilled would have been further motivated

to utilize the dervatized lipase in a detergent composition as taught in '438 patent (claim 37 and 38). Olesen *et al.* provide one of ordinary skill in the art with further motivation to utlize lipase to prepare dough and baked products as they teach that the addition of lipase to dough ingredient improves the dough properties (claims 38 and 39).

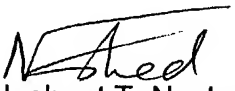
Claims 34 is free of prior art.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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